## Remarks

Applicants respectfully request reconsideration of this application in view of the above amendments and the following remarks.

1. Status of the Claims

Claims 22-23 were pending in this application, of which Claims 22, 26, 28, and 32 have been amended and Claims 25 and 31 have been canceled. Upon entry of the above amendments, Claims 22-24, 26-30, and 32-33 will be pending in this application.

2. Amendments to the Claims

The subject matter of original Claim 25 has been incorporated into Claim 22 and thus amended Claim 22 corresponds to original Claim 25. Similarly, the subject matter of original Claim 31 has been incorporated into Claim 28.

No new matter has been added. Entry of the amendments to the claims is respectfully requested.

3. Rejection of Claims 22-33 under 35 U.S.C. §112(1)

Claims 22-33 were rejected under 35 U.S.C. §112, first paragraph as not being fully enabled. Applicants respectfully traverse the rejection.

Section 112, first paragraph requires, in part, that the specification contain a written description of the invention which enables "any person skilled in the art to which it pertains ... to make and use" the invention.

The present claims are directed to methods of treatment, as recited, for example, in Claim 22, "the method comprising administering to a patient in need of treatment a therapeutically effective amount of a compound of formula (Ia) ..." or in Claim 28, "the method comprising administering to a patient in need of treatment a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceuticlaly aceeptable diluent or carrier and a compound of formula (Ia) ...". Practicing the claimed invention, therefore, requires

(1) preparing a compound of formula (Ia), or a pharmaceutical composition comprising a compound of formula (Ia) and (2) administering the compound or composition to a patient.

The present specification provides an enabling disclosure of the processes of preparing and administering a compound of formula (Ia) or a composition comprising such a compound. In particular, the specification discloses processes for preparing the compound at page 9 line 20 to page 12, line 2 and in the synthetic examples at pages 16-21. The pharmaceutical compositions and methods of administration are conventional and well known to a person skilled in the art. The disclosure of the pharmaceutical compositions and administration thereof at page 12, line 7 to page 15, line 37 of the specification enables a person skilled in the art to formulate the composition and administer the present compound or composition to a patient. Applicants respectfully submit, therefore, that Claims 22 and 28, and claims dependent therefrom, are fully enabled by the present specification.

The analysis of the Office Action, in contrast, in paragraph 5, pages 2-6, appears to be directed not to whether the practice of the invention is *enabled* but rather to whether the *utility* of the claimed invention has been established. For example, the Office action states: "The efficacy of an individual compound against a specific disease or symptom needs to be *specifically and individually* supported by factual evidence." (Office Action, page 4, lines 12-14, emphasis added.) In this regard, the Examiner appears to be imposing under 35 U.S.C. §112(1), a requirement for proof of therapeutic or pharmacological utility, which the MPEP cautions may not be imposed under 35 U.S.C. §101. MPEP §2107.01 (III) counsels "Inventions asserted to have utility in the treatment of human or animal disorders are subject to the same legal requirements for utility as inventions in any other field of technology. *In re Chilowsky*, 229 F.2d 457, 461-2, 108 USPQ 321, 325 (CCPA 1956) ('There appears to be no basis in the statutes or decisions for requiring any more conclusive evidence of operativeness in one type of case than another ..."

While traversing the imposition of such a utility standard under 35 U.S.C. §112(1), Applicants respectfully submit the specification together with the state of the art at the time the application was filed fully supports the breadth of the claims now presented.

With regard to assessing therapeutic utility, MPEP §2107.03 (I) states "As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant

to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility" and that an applicant can establish this reasonable correlation by "statistically relevant data, ... arguments or reasoning, documentary evidence (e.g. articles in scientific journals), or any combination thereof." MPEP §2107.03 (III) points out that data from *in vitro* or animal testing is generally sufficient to support therapeutic utility.

In the present case, the specification discloses *functional* assays for inhibition of the receptor tyrosine kinases VEGFR, PDGFR. c-Kit, and Flt-3 (page 25, line 9 to page 27, line 13) and reports that compounds exemplified "have been found to exhibit an $IC_{50}$ of less than 10 μM in one or more of the above assays." In particular, the compound 3-[3,5-dimethyl-4-(3-oxo-3-piperazin-1-ylpropyl)-1H-pyrrol-2-ylmethylene]-1,3-dihydroindol-2-one, i.e. the compound of formula (Ia) wherein R is hydrogen, was reported to be a "highly potent and selective inhibitor of PDGFR, c-Kit, VEGFR, and Flt-3." (page 9, lines 8-9).

A correlation between receptor tyrosine kinases and proliferative disorders including cancer was established in the scientific literature at the time the present application was filed. For example, Zwick *et al.*, "Receptor tyrosine kinase signalling as a target for cancer intervention strategies," *Endocrine-Related Cancer* (2001) **8** 161-173, report "it is well known that aberrant signalling by RTKs [receptor tyrosine kinases] is critically involved in human cancer and other hyper-proliferative diseases." (page 161, col. 2, lines 12-14) and "Another promising approach to inhibit aberrant RTK signalling are small molecule drugs that selectively interfere with the intrinisic tyrosine kinase activity and thereby block receptor autophosphorylation and activation of downstream signal transducers." (page 163, col. 1, bottom paragraph)

The PCT publication WO 99/61422 and equivalent U.S. Patent No. 6,395,734, [hereafter '734] both of record, provide an extended discussion of receptor tyrosine kinases and the use of inhibitors thereof as a therapeutic approach to treat solid tumors, non-solid tumor cancers and other cell proliferative disorders. ('734, col. 75, line 6 to col. 81, line 46, in particular, col. 76, line 54 to col. 77, line 25, where the equivalent '734 patent has been cited for convenience). As cited therein, the VEGF receptor tyrosine kinase is associated with the processes of vasculogenesis and angiogenesis, which processes play a pivotal role in cancer development. Thus, inhibition of the VEGF receptor tyrosine kinase is reported as a therapeutic approach to the

treatment of many kinds of solid tumors and other proliferative diseases such as hemangioma, restenosis and diabetic retinopathy. ('734 col. 78, lines 46-61)

The ability of inhibitors of the receptor tyrosine kinases VEGFR and PDGFR to inhibit the growth of solid tumors and suppress retinal angiogenesis in animal models was widely reported at the time the application was filed. See, for example, the articles by Sun *et al. J Med. Chem.* **2000**, *43*, 2655-2663; Fong *et al.*, *Cancer Research*, **1999**, *59*, 99-106; Laird *et al.*, *Cancer Research*, **2000**, *60*, 4152-4160; Drevs *et al.*, *Cancer Research*, **2000**, *60*, 4819-4824; Wood, *Medicina*, **2000**, *60 (Suppl.II)*, 41-47; and Aiello *et al.*, *Proc. Natl. Acad. Sci.*, **1995**, *92*, 10457-10461.

In addition, Applicants bring to the Examiner's attention data on the *in vivo* anti-tumor activity of the compound SU11248 whose activity is similar to that of compounds of the present invention, i.e. like 3-[3,5-dimethyl-4-(3-oxo-3-piperazin-1-ylpropyl)-1H-pyrrol-2-ylmethylene]-1,3-dihydroindol-2-one , SU11248 is an inhibitor of the VEGFR PDGFR Kit and Flt-3 receptor tyrosine kinases. Mendel *et al.*, *Clinical Cancer Research,* **2003**, *9*, 327-337, report: "In mouse xenograft models, SU11248 exhibited broad and potent antitumor activity, causing regression, growth arrest or substantially reduced growth of various established xenografts derived from human or rat tumor cell lines." (abstract, lines 13-16).

In summary, the practice of the methods of treatment of the invention are completely enabled by the specification. Furthermore, the compounds of the present invention have been shown to inhibit the VEGFR PDGFR Kit and Flt-3 receptor tyrosine kinases. A correlation between inhibition of the VEGFR PDGFR Kit and Flt-3 receptor tyrosine kinases and the treatment of proliferative disorders including cancer and, in particular, solid tumors was known in the art at the time the application was filed. Accordingly, Applicants respectfully submit, Claims 22-24, 26-30, and 32-33 as currently presented satisfy all requirements of 35 U.S.C. §112(1) and, consequently, the present rejection may be withdrawn.

4. Rejection of Claims 22 and 28 under 35 U.S.C. §112(1)

Claims 22 and 28 were also rejected under 35 U.S.C. §112, first paragraph as being reach-through claims. The amendments to Claims 22 and 28 render this rejection moot and accordingly the rejection can be withdrawn.

5. Rejection of Claims 22-24 and 28-30 under 35 U.S.C. §112(2)

Claims 22-24 and 28-30 were also rejected under 35 U.S.C. §112, second paragraph. As described above, the correlation between inhibition of receptor tyrosine kinases and treatment of proliferative disorders including cancer and, in particular, solid tumors had been established in the state of the art at the time the application was filed. Accordingly there is no lack of clarity in the language of Claims 22-24 and 28-30, as presently presented. Consequently, Claims 22-24 and 28-30 satisfy the requirements of 35 U.S.C. §112(2) and the present rejection may be withdrawn.

6. Rejection of Claims 22 and 28 under 35 U.S.C. §101

Claims 22 and 28 were also rejected under 35 U.S.C. §101 as being reach-through claims. The amendments to Claims 22 and 28 render this rejection moot and accordingly the rejection can be withdrawn.

7. Conclusion

In view of the foregoing, Applicants respectfully submit Claims 22-24 and 28-30, the claims currently pending in the application, are in condition for allowance. Reconsideration and prompt passage of the application to allowance is respectfully requested. Should there be any issues regarding this application that can be resolved by telephone, the examiner is invited to telephone the undersigned agent for Applicants at (650) 808-3764 (direct).

Respectfully submitted,

Date: May 6, 2005

By: Roberta P. Saxon

Roberta P. Saxon, Ph.D.
Reg. No. 43,087

THERAVANCE, INC.
901 Gateway Boulevard
South San Francisco, CA 94080
Tel: (650) 808-6000
Fax: (650) 808-6078